

### **Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

### **Listing of Claims:**

Claim 1. (Canceled)

Claim 2. (Canceled)

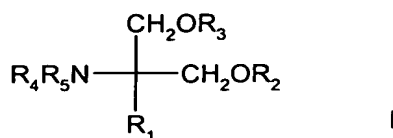
Claim 3. (Original) A pharmaceutical composition for use in the treatment of chronic heart failure, congestive heart failure, arrhythmia or tachyarrhythmia, unstable angina, acute myocardial infarction or complications from cardiac surgery or for improving heart energy efficiency or cardiac output, comprising a S1P receptor agonist together with one or more pharmaceutically acceptable diluents or carriers therefor.

Claim 4. (Original) A method for treating chronic heart failure, congestive heart failure, arrhythmia or tachyarrhythmia, unstable angina, acute myocardial infarction or complications from cardiac surgery or for improving heart energy efficiency or cardiac output in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a S1P receptor agonist.

Claim 5. (Original) A pharmaceutical combination comprising a) a first agent which is a S1P receptor agonist, and b) a co-agent selected from an angiotension converting enzyme inhibitor, an angiotension II receptor antagonist, a synthetic form of B-type natriuretic peptide (BNP) or other human B-type natriuretic peptide, a  $\beta$ -blocker, a  $\beta$ -adrenergic receptor agonist, an  $\alpha$ -2 receptor agonist, a calcium antagonist and a diuretic.

Claim 6. (Original) A method according to claim 4 comprising co-administration concomitantly or in sequence, of a therapeutically effective amount of a S1P receptor agonist and a co-agent selected from an angiotension converting enzyme inhibitor, an angiotension II receptor antagonist, a synthetic form of B-type natriuretic peptide (BNP) or other human B-type natriuretic peptide, a  $\beta$ -blocker, a  $\beta$ -adrenergic receptor agonist, an  $\alpha$ -2 receptor agonist, a calcium antagonist and a diuretic.

Claim 7. (Currently amended) ~~Use, a pharmaceutical composition, a pharmaceutical combination or a method according to claims 1 to 6~~ The composition of claim 3, wherein the S1P receptor agonist is selected from a compound of formula I



wherein R<sub>1</sub> is a straight- or branched (C<sub>12-22</sub>)carbon chain

- which may have in the chain a bond or a hetero atom selected from a double bond, a triple bond, O, S, NR<sub>6</sub>, wherein R<sub>6</sub> is H, alkyl, aralkyl, acyl or alkoxy carbonyl, and carbonyl, and/or
- which may have as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxy carbonyl, alkoxy carbonylamino, acyloxy, alkyl carbamoyl, nitro, halogen, amino, hydroxyimino, hydroxy or carboxy; or

R<sub>1</sub> is

- a phenylalkyl wherein alkyl is a straight- or branched (C<sub>6-20</sub>)carbon chain or
- a phenylalkyl wherein alkyl is a straight- or branched (C<sub>1-30</sub>)carbon chain wherein said phenylalkyl is substituted by
- a straight- or branched (C<sub>6-20</sub>)carbon chain optionally substituted by halogen,
- a straight- or branched (C<sub>6-20</sub>)alkoxy chain optionally substituted by halogen,
- a straight- or branched (C<sub>6-20</sub>)alkenyloxy,
- phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl,
- cycloalkylalkyl substituted by C<sub>6-20</sub>alkyl,
- heteroarylalkyl substituted by C<sub>6-20</sub>alkyl,
- heterocyclic C<sub>6-20</sub>alkyl or
- heterocyclic alkyl substituted by C<sub>6-20</sub>alkyl,

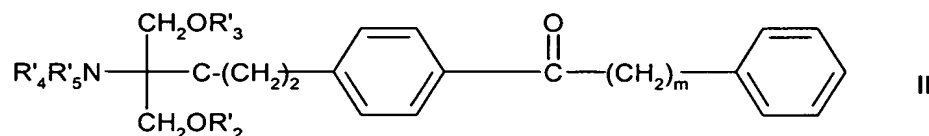
and wherein

the alkyl moiety may have

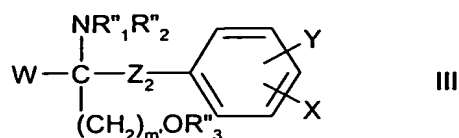
- in the carbon chain, a bond or a heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or NR<sub>6</sub>, wherein R<sub>6</sub> is as defined above, and
- as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxy carbonyl, alkoxy carbonylamino, acyloxy, alkyl carbamoyl, nitro, halogen, amino, hydroxy or carboxy, and

each of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub>, independently, is H, C<sub>1-4</sub>alkyl or acyl;

a compound of formula II



wherein m is 1 to 9 and each of R'<sub>2</sub>, R'<sub>3</sub>, R'<sub>4</sub> and R'<sub>5</sub>, independently, is H, alkyl or acyl, a compound of formula III

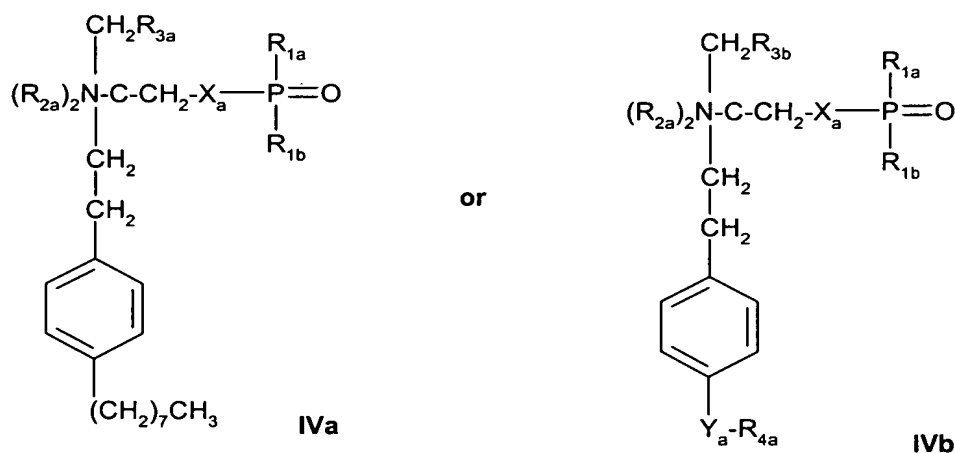


wherein W is H; C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkynyl; unsubstituted or by OH substituted phenyl; R''<sub>4</sub>O(CH<sub>2</sub>)<sub>n</sub>; or C<sub>1-6</sub>alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C<sub>3-8</sub>cycloalkyl, phenyl and phenyl substituted by OH;

X is H or unsubstituted or substituted straight chain alkyl having a number p of carbon atoms or unsubstituted or substituted straight chain alkoxy having a number (p-1) of carbon atoms, e.g. substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub>alkyl, OH, C<sub>1-6</sub>alkoxy, acyloxy, amino, C<sub>1-6</sub>alkylamino, acylamino, oxo, haloC<sub>1-6</sub>alkyl, halogen, unsubstituted phenyl and phenyl substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub>alkyl, OH, C<sub>1-6</sub>alkoxy, acyl, acyloxy, amino, C<sub>1-6</sub>alkylamino, acylamino, haloC<sub>1-6</sub>alkyl and halogen; Y is H, C<sub>1-6</sub>alkyl, OH, C<sub>1-6</sub>alkoxy, acyl, acyloxy, amino, C<sub>1-6</sub>alkylamino, acylamino, haloC<sub>1-6</sub>alkyl or halogen, Z<sub>2</sub> is a single bond or a straight chain alkylene having a number of carbon atoms of q, each of p and q, independently, is an integer of 1 to 20, with the proviso of 6 ≤ p+q ≤ 23, m' is 1, 2 or 3, n is 2 or 3,

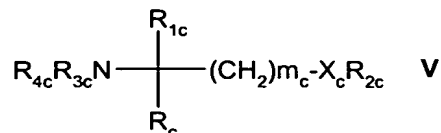
each of R''<sub>1</sub>, R''<sub>2</sub>, R''<sub>3</sub> and R''<sub>4</sub>, independently, is H, C<sub>1-4</sub>alkyl or acyl;

a compound of formula IVa or IVb



wherein X<sub>a</sub> is O, S, NR<sub>1s</sub> or a group -(CH<sub>2</sub>)<sub>na</sub>-, which group is unsubstituted or substituted by 1 to 4 halogen; n<sub>a</sub> is 1 or 2, R<sub>1s</sub> is H or (C<sub>1-4</sub>)alkyl, which alkyl is unsubstituted or substituted by halogen; R<sub>1a</sub> is H, OH, (C<sub>1-4</sub>)alkyl or O(C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by 1 to 3 halogen; R<sub>1b</sub> is H, OH or (C<sub>1-4</sub>)alkyl, wherein alkyl is unsubstituted or substituted by halogen; each R<sub>2a</sub> is independently selected from H or (C<sub>1-4</sub>)alkyl, which alkyl is unsubstituted or substituted by halogen; R<sub>3a</sub> is H, OH, halogen or O(C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by halogen; and R<sub>3b</sub> is H, OH, halogen, (C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by hydroxy, or O(C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by halogen; Y<sub>a</sub> is -CH<sub>2</sub>-, -C(O)-, -CH(OH)-, -C(=NOH)-, O or S, and R<sub>4a</sub> is (C<sub>4-14</sub>)alkyl or (C<sub>4-14</sub>)alkenyl; and

a compound of formula V



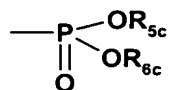
wherein

$m_c$  is 1, 2 or 3;

$X_c$  is O or a direct bond;

$R_{1c}$  is H; C1-6alkyl optionally substituted by OH, acyl, halogen, C3-10cycloalkyl, phenyl or hydroxy-phenylene; C2-6alkenyl; C2-6alkynyl; or phenyl optionally substituted by OH;

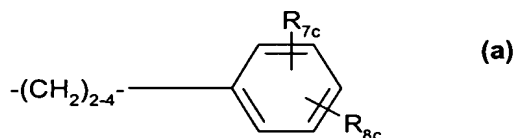
$R_{2c}$  is



wherein  $R_{5c}$  is H or C<sub>1-4</sub>alkyl optionally substituted by 1, 2 or 3 halogen atoms, and  $R_{6c}$  is H or C<sub>1-4</sub>alkyl optionally substituted by halogen;

each of  $R_{3c}$  and  $R_{4c}$ , independently, is H, C<sub>1-4</sub>alkyl optionally substituted by halogen, or acyl, and

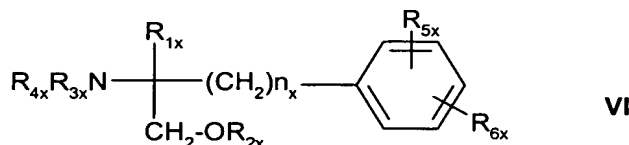
$R_c$  is C<sub>13-20</sub>alkyl which may optionally have in the chain an oxygen atom and which may optionally be substituted by nitro, halogen, amino, hydroxy or carboxy; or a residue of formula (a)



wherein  $R_{7c}$  is H, C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkoxy, and  $R_{8c}$  is substituted C<sub>1-20</sub>alkanoyl, phenylC<sub>1-14</sub>alkyl wherein the C<sub>1-14</sub>alkyl is optionally substituted by halogen or OH, cycloalkylC<sub>1-14</sub>alkoxy or phenylC<sub>1-14</sub>alkoxy wherein the cycloalkyl or phenyl ring is optionally substituted by halogen, C<sub>1-4</sub>alkyl and/or C<sub>1-4</sub>alkoxy, phenylC<sub>1-14</sub>alkoxy-C<sub>1-14</sub>alkyl, phenoxyC<sub>1-14</sub>alkoxy or phenoxyC<sub>1-14</sub>alkyl,

$R_c$  being also a residue of formula (a) wherein  $R_{8c}$  is C<sub>1-14</sub>alkoxy when  $R_{1c}$  is C<sub>1-4</sub>alkyl, C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkynyl,

or a compound of formula VI



wherein

$n_x$  is 2, 3 or 4

R<sub>1x</sub> is H; C<sub>1-6</sub>alkyl optionally substituted by OH, acyl, halogen, cycloalkyl, phenyl or hydroxy-phenylene; C<sub>2-6</sub>alkenyl; C<sub>2-6</sub>alkynyl; or phenyl optionally substituted by OH;

R<sub>2x</sub> is H, C<sub>1-4</sub>alkyl or acyl

each of R<sub>3x</sub> and R<sub>4x</sub>, independently, is H, C<sub>1-4</sub>alkyl optionally substituted by halogen or acyl,

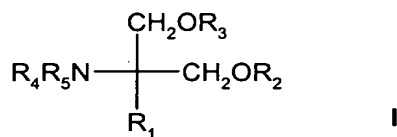
R<sub>5x</sub> is H, C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkoxy, and

R<sub>6x</sub> is C<sub>1-20</sub>alkanoyl substituted by cycloalkyl; cycloalkylC<sub>1-14</sub>alkoxy wherein the cycloalkyl ring is optionally substituted by halogen, C<sub>1-4</sub>alkyl and/or C<sub>1-4</sub>alkoxy; phenylC<sub>1-14</sub>alkoxy wherein the phenyl ring is optionally substituted by halogen, C<sub>1-4</sub>alkyl and/or C<sub>1-4</sub>alkoxy,

R<sub>6x</sub> being also C<sub>4-14</sub>alkoxy when R<sub>1x</sub> is C<sub>2-4</sub>alkyl substituted by OH, pentyloxy or hexyloxy when R<sub>1x</sub> is C<sub>1-4</sub>alkyl,

provided that R<sub>6x</sub> is other than phenyl-butylenoxy when either R<sub>5x</sub> is H or R<sub>1x</sub> is methyl, or a pharmaceutically acceptable salt thereof.

Claim 8. (New) The method of claim 4, wherein the S1P receptor agonist is selected from a compound of formula I



wherein R<sub>1</sub> is a straight- or branched (C<sub>12-22</sub>)carbon chain

- which may have in the chain a bond or a hetero atom selected from a double bond, a triple bond, O, S, NR<sub>6</sub>, wherein R<sub>6</sub> is H, alkyl, aralkyl, acyl or alkoxycarbonyl, and carbonyl, and/or
- which may have as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxyimino, hydroxy or carboxy; or

R<sub>1</sub> is

- a phenylalkyl wherein alkyl is a straight- or branched (C<sub>6-20</sub>)carbon chain or
- a phenylalkyl wherein alkyl is a straight- or branched (C<sub>1-30</sub>)carbon chain wherein said phenylalkyl is substituted by
- a straight- or branched (C<sub>6-20</sub>)carbon chain optionally substituted by halogen,
- a straight- or branched (C<sub>6-20</sub>)alkoxy chain optionally substituted by halogen,
- a straight- or branched (C<sub>6-20</sub>)alkenyloxy,
- phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl,
- cycloalkylalkyl substituted by C<sub>6-20</sub>alkyl,
- heteroarylalkyl substituted by C<sub>6-20</sub>alkyl,
- heterocyclic C<sub>6-20</sub>alkyl or
- heterocyclic alkyl substituted by C<sub>6-20</sub>alkyl,

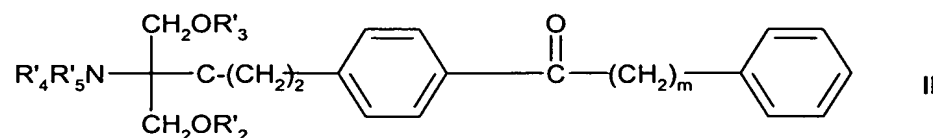
and wherein

the alkyl moiety may have

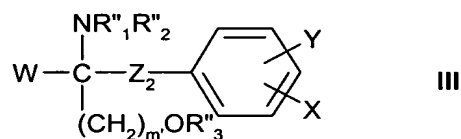
- in the carbon chain, a bond or a heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or  $\text{NR}_6$ , wherein  $\text{R}_6$  is as defined above, and
- as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxy or carboxy, and

each of  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$  and  $\text{R}_5$ , independently, is H,  $\text{C}_{1-4}$ alkyl or acyl;

a compound of formula II



wherein  $m$  is 1 to 9 and each of  $\text{R}'_2$ ,  $\text{R}'_3$ ,  $\text{R}'_4$  and  $\text{R}'_5$ , independently, is H, alkyl or acyl, a compound of formula III

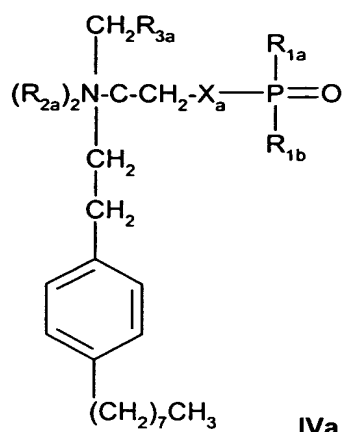


wherein  $W$  is H;  $\text{C}_{1-6}$ alkyl,  $\text{C}_{2-6}$ alkenyl or  $\text{C}_{2-6}$ alkynyl; unsubstituted or by OH substituted phenyl;  $\text{R}''_4\text{O}(\text{CH}_2)_n$ ; or  $\text{C}_{1-6}$ alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen,  $\text{C}_{3-8}$ cycloalkyl, phenyl and phenyl substituted by OH;

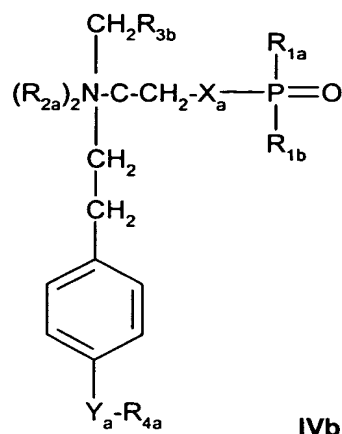
$X$  is H or unsubstituted or substituted straight chain alkyl having a number  $p$  of carbon atoms or unsubstituted or substituted straight chain alkoxy having a number  $(p-1)$  of carbon atoms, e.g. substituted by 1 to 3 substituents selected from the group consisting of  $\text{C}_{1-6}$ alkyl, OH,  $\text{C}_{1-6}$ alkoxy, acyloxy, amino,  $\text{C}_{1-6}$ alkylamino, acylamino, oxo, halo $\text{C}_{1-6}$ alkyl, halogen, unsubstituted phenyl and phenyl substituted by 1 to 3 substituents selected from the group consisting of  $\text{C}_{1-6}$ alkyl, OH,  $\text{C}_{1-6}$ alkoxy, acyl, acyloxy, amino,  $\text{C}_{1-6}$ alkylamino, acylamino, halo $\text{C}_{1-6}$ alkyl and halogen;  $Y$  is H,  $\text{C}_{1-6}$ alkyl, OH,  $\text{C}_{1-6}$ alkoxy, acyl, acyloxy, amino,  $\text{C}_{1-6}$ alkylamino, acylamino, halo $\text{C}_{1-6}$ alkyl or halogen,  $Z_2$  is a single bond or a straight chain alkylene having a number of carbon atoms of  $q$ , each of  $p$  and  $q$ , independently, is an integer of 1 to 20, with the proviso of  $6 \leq p+q \leq 23$ ,  $m'$  is 1, 2 or 3,  $n$  is 2 or 3,

each of  $\text{R}''_1$ ,  $\text{R}''_2$ ,  $\text{R}''_3$  and  $\text{R}''_4$ , independently, is H,  $\text{C}_{1-4}$ alkyl or acyl;

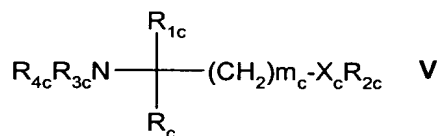
a compound of formula IVa or IVb



or



wherein  $\text{X}_a$  is O, S,  $\text{NR}_{1s}$  or a group  $-(\text{CH}_2)_{n_a}-$ , which group is unsubstituted or substituted by 1 to 4 halogen;  $n_a$  is 1 or 2,  $\text{R}_{1s}$  is H or  $(\text{C}_{1-4})$ alkyl, which alkyl is unsubstituted or substituted by halogen;  $\text{R}_{1a}$  is H, OH,  $(\text{C}_{1-4})$ alkyl or  $\text{O}(\text{C}_{1-4})$ alkyl wherein alkyl is unsubstituted or substituted by 1 to 3 halogen;  $\text{R}_{1b}$  is H, OH or  $(\text{C}_{1-4})$ alkyl, wherein alkyl is unsubstituted or substituted by halogen; each  $\text{R}_{2a}$  is independently selected from H or  $(\text{C}_{1-4})$ alkyl, which alkyl is unsubstituted or substituted by halogen;  $\text{R}_{3a}$  is H, OH, halogen or  $\text{O}(\text{C}_{1-4})$ alkyl wherein alkyl is unsubstituted or substituted by halogen; and  $\text{R}_{3b}$  is H, OH, halogen,  $(\text{C}_{1-4})$ alkyl wherein alkyl is unsubstituted or substituted by hydroxy, or  $\text{O}(\text{C}_{1-4})$ alkyl wherein alkyl is unsubstituted or substituted by halogen;  $\text{Y}_a$  is  $-\text{CH}_2-$ ,  $-\text{C}(\text{O})-$ ,  $-\text{CH}(\text{OH})-$ ,  $-\text{C}(=\text{NOH})-$ , O or S, and  $\text{R}_{4a}$  is  $(\text{C}_{4-14})$ alkyl or  $(\text{C}_{4-14})$ alkenyl; and a compound of formula V



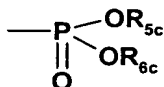
wherein

$m_c$  is 1, 2 or 3;

$\text{X}_c$  is O or a direct bond;

$\text{R}_{1c}$  is H; C1-6alkyl optionally substituted by OH, acyl, halogen, C3-10cycloalkyl, phenyl or hydroxy-phenylene; C2-6alkenyl; C2-6alkynyl; or phenyl optionally substituted by OH;

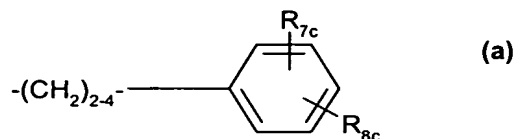
$\text{R}_{2c}$  is



wherein  $\text{R}_{5c}$  is H or  $\text{C}_{1-4}$ alkyl optionally substituted by 1, 2 or 3 halogen atoms, and  $\text{R}_{6c}$  is H or  $\text{C}_{1-4}$ alkyl optionally substituted by halogen;

each of  $\text{R}_{3c}$  and  $\text{R}_{4c}$ , independently, is H,  $\text{C}_{1-4}$ alkyl optionally substituted by halogen, or acyl, and

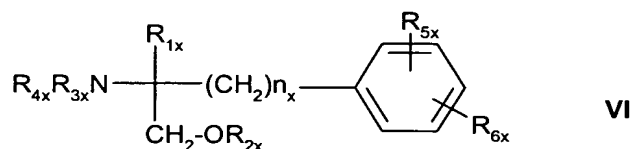
$R_c$  is  $C_{13-20}$ alkyl which may optionally have in the chain an oxygen atom and which may optionally be substituted by nitro, halogen, amino, hydroxy or carboxy; or a residue of formula (a)



wherein  $R_{7c}$  is H,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkoxy, and  $R_{8c}$  is substituted  $C_{1-20}$ alkanoyl, phenyl $C_{1-14}$ alkyl wherein the  $C_{1-14}$ alkyl is optionally substituted by halogen or OH, cycloalkyl $C_{1-14}$ alkoxy or phenyl $C_{1-14}$ alkoxy wherein the cycloalkyl or phenyl ring is optionally substituted by halogen,  $C_{1-4}$ alkyl and/or  $C_{1-4}$ alkoxy, phenyl $C_{1-14}$ alkoxy- $C_{1-14}$ alkyl, phenoxy $C_{1-14}$ alkoxy or phenoxy $C_{1-14}$ alkyl,

$R_c$  being also a residue of formula (a) wherein  $R_{8c}$  is  $C_{1-14}$ alkoxy when  $R_{1c}$  is  $C_{1-4}$ alkyl,  $C_{2-6}$ alkenyl or  $C_{2-6}$ alkynyl,

or a compound of formula VI



wherein

$n_x$  is 2, 3 or 4

$R_{1x}$  is H;  $C_{1-6}$ alkyl optionally substituted by OH, acyl, halogen, cycloalkyl, phenyl or hydroxy-phenylene;  $C_{2-6}$ alkenyl;  $C_{2-6}$ alkynyl; or phenyl optionally substituted by OH;

$R_{2x}$  is H,  $C_{1-4}$ alkyl or acyl

each of  $R_{3x}$  and  $R_{4x}$ , independently, is H,  $C_{1-4}$ alkyl optionally substituted by halogen or acyl,

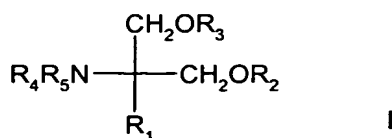
$R_{5x}$  is H,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkoxy, and

$R_{6x}$  is  $C_{1-20}$ alkanoyl substituted by cycloalkyl; cycloalkyl $C_{1-14}$ alkoxy wherein the cycloalkyl ring is optionally substituted by halogen,  $C_{1-4}$ alkyl and/or  $C_{1-4}$ alkoxy; phenyl $C_{1-14}$ alkoxy wherein the phenyl ring is optionally substituted by halogen,  $C_{1-4}$ alkyl and/or  $C_{1-4}$ alkoxy,

$R_{6x}$  being also  $C_{4-14}$ alkoxy when  $R_{1x}$  is  $C_{2-4}$ alkyl substituted by OH, pentyloxy or hexyloxy when  $R_{1x}$  is  $C_{1-4}$ alkyl,

provided that  $R_{6x}$  is other than phenyl-butylenoxy when either  $R_{5x}$  is H or  $R_{1x}$  is methyl, or a pharmaceutically acceptable salt thereof.

Claim 9. (New) The pharmaceutical combination of claim 5, wherein the S1P receptor agonist is selected from a compound of formula I



wherein R<sub>1</sub> is a straight- or branched (C<sub>12-22</sub>)carbon chain

- which may have in the chain a bond or a hetero atom selected from a double bond, a triple bond, O, S, NR<sub>6</sub>, wherein R<sub>6</sub> is H, alkyl, aralkyl, acyl or alkoxycarbonyl, and carbonyl, and/or
- which may have as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyle, nitro, halogen, amino, hydroxyimino, hydroxy or carboxy; or

R<sub>1</sub> is

- a phenylalkyl wherein alkyl is a straight- or branched (C<sub>6-20</sub>)carbon chain or
- a phenylalkyl wherein alkyl is a straight- or branched (C<sub>1-30</sub>)carbon chain wherein said phenylalkyl is substituted by
- a straight- or branched (C<sub>6-20</sub>)carbon chain optionally substituted by halogen,
- a straight- or branched (C<sub>6-20</sub>)alkoxy chain optionally substituted by halogen,
- a straight- or branched (C<sub>6-20</sub>)alkenyloxy,
- phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl,
- cycloalkylalkyl substituted by C<sub>6-20</sub>alkyl,
- heteroarylalkyl substituted by C<sub>6-20</sub>alkyl,
- heterocyclic C<sub>6-20</sub>alkyl or
- heterocyclic alkyl substituted by C<sub>6-20</sub>alkyl,

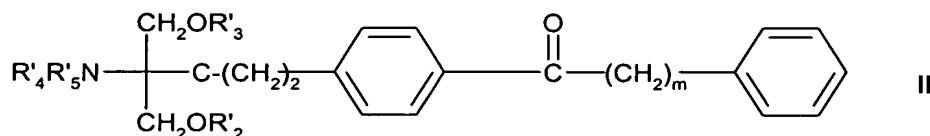
and wherein

the alkyl moiety may have

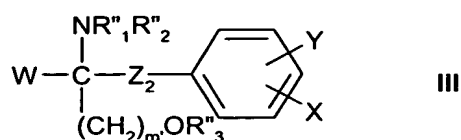
- in the carbon chain, a bond or a heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or NR<sub>6</sub>, wherein R<sub>6</sub> is as defined above, and
- as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyle, nitro, halogen, amino, hydroxy or carboxy, and

each of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub>, independently, is H, C<sub>1-4</sub>alkyl or acyl;

a compound of formula II



wherein m is 1 to 9 and each of R'<sub>2</sub>, R'<sub>3</sub>, R'<sub>4</sub> and R'<sub>5</sub>, independently, is H, alkyl or acyl, a compound of formula III

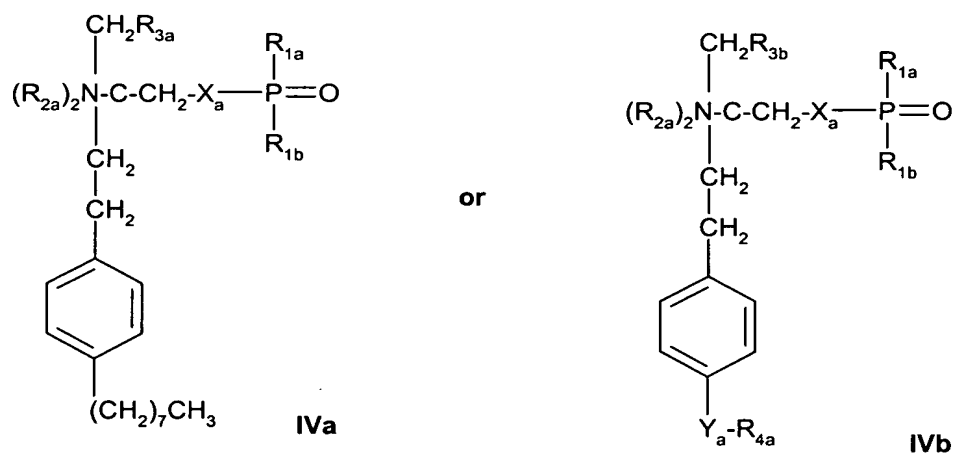


wherein W is H; C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkynyl; unsubstituted or by OH substituted phenyl; R''<sub>4</sub>O(CH<sub>2</sub>)<sub>n</sub>; or C<sub>1-6</sub>alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C<sub>3-8</sub>cycloalkyl, phenyl and phenyl substituted by OH;

X is H or unsubstituted or substituted straight chain alkyl having a number p of carbon atoms or unsubstituted or substituted straight chain alkoxy having a number (p-1) of carbon atoms, e.g. substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub>alkyl, OH, C<sub>1-6</sub>alkoxy, acyloxy, amino, C<sub>1-6</sub>alkylamino, acylamino, oxo, haloC<sub>1-6</sub>alkyl, halogen, unsubstituted phenyl and phenyl substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub>alkyl, OH, C<sub>1-6</sub>alkoxy, acyl, acyloxy, amino, C<sub>1-6</sub>alkylamino, acylamino, haloC<sub>1-6</sub>alkyl and halogen; Y is H, C<sub>1-6</sub>alkyl, OH, C<sub>1-6</sub>alkoxy, acyl, acyloxy, amino, C<sub>1-6</sub>alkylamino, acylamino, haloC<sub>1-6</sub>alkyl or halogen, Z<sub>2</sub> is a single bond or a straight chain alkylene having a number of carbon atoms of q, each of p and q, independently, is an integer of 1 to 20, with the proviso of 6 ≤ p+q ≤ 23, m' is 1, 2 or 3, n is 2 or 3,

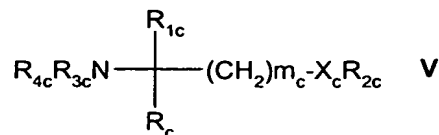
each of R''<sub>1</sub>, R''<sub>2</sub>, R''<sub>3</sub> and R''<sub>4</sub>, independently, is H, C<sub>1-4</sub>alkyl or acyl;

a compound of formula IVa or IVb



wherein X<sub>a</sub> is O, S, NR<sub>1s</sub> or a group -(CH<sub>2</sub>)<sub>na</sub>-, which group is unsubstituted or substituted by 1 to 4 halogen; n<sub>a</sub> is 1 or 2, R<sub>1s</sub> is H or (C<sub>1-4</sub>)alkyl, which alkyl is unsubstituted or substituted by halogen; R<sub>1a</sub> is H, OH, (C<sub>1-4</sub>)alkyl or O(C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by 1 to 3 halogen; R<sub>1b</sub> is H, OH or (C<sub>1-4</sub>)alkyl, wherein alkyl is unsubstituted or substituted by halogen; each R<sub>2a</sub> is independently selected from H or (C<sub>1-4</sub>)alkyl, which alkyl is unsubstituted or substituted by halogen; R<sub>3a</sub> is H, OH, halogen or O(C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by halogen; and R<sub>3b</sub> is H, OH, halogen, (C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by hydroxy, or O(C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by halogen; Y<sub>a</sub> is -CH<sub>2</sub>-, -C(O)-, -CH(OH)-, -C(=NOH)-, O or S, and R<sub>4a</sub> is (C<sub>4-14</sub>)alkyl or (C<sub>4-14</sub>)alkenyl; and

a compound of formula V



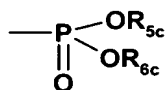
wherein

$m_c$  is 1, 2 or 3;

$X_c$  is O or a direct bond;

$R_{1c}$  is H; C1-6alkyl optionally substituted by OH, acyl, halogen, C3-10cycloalkyl, phenyl or hydroxy-phenylene; C2-6alkenyl; C2-6alkynyl; or phenyl optionally substituted by OH;

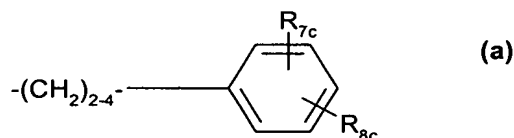
$R_{2c}$  is



wherein  $R_{5c}$  is H or C<sub>1-4</sub>alkyl optionally substituted by 1, 2 or 3 halogen atoms, and  $R_{6c}$  is H or C<sub>1-4</sub>alkyl optionally substituted by halogen;

each of  $R_{3c}$  and  $R_{4c}$ , independently, is H, C<sub>1-4</sub>alkyl optionally substituted by halogen, or acyl, and

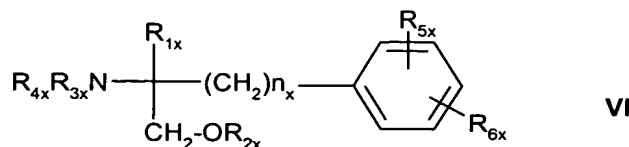
$R_c$  is C<sub>13-20</sub>alkyl which may optionally have in the chain an oxygen atom and which may optionally be substituted by nitro, halogen, amino, hydroxy or carboxy; or a residue of formula (a)



wherein  $R_{7c}$  is H, C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkoxy, and  $R_{8c}$  is substituted C<sub>1-20</sub>alkanoyl, phenylC<sub>1-14</sub>alkyl wherein the C<sub>1-14</sub>alkyl is optionally substituted by halogen or OH, cycloalkylC<sub>1-14</sub>alkoxy or phenylC<sub>1-14</sub>alkoxy wherein the cycloalkyl or phenyl ring is optionally substituted by halogen, C<sub>1-4</sub>alkyl and/or C<sub>1-4</sub>alkoxy, phenylC<sub>1-14</sub>alkoxy-C<sub>1-14</sub>alkyl, phenoxyC<sub>1-14</sub>alkoxy or phenoxyC<sub>1-14</sub>alkyl,

$R_c$  being also a residue of formula (a) wherein  $R_{8c}$  is C<sub>1-14</sub>alkoxy when  $R_{1c}$  is C<sub>1-4</sub>alkyl, C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkynyl,

or a compound of formula VI



wherein

$n_x$  is 2, 3 or 4

R<sub>1x</sub> is H; C<sub>1-6</sub>alkyl optionally substituted by OH, acyl, halogen, cycloalkyl, phenyl or hydroxyphenylene; C<sub>2-6</sub>alkenyl; C<sub>2-6</sub>alkynyl; or phenyl optionally substituted by OH;

R<sub>2x</sub> is H, C<sub>1-4</sub>alkyl or acyl

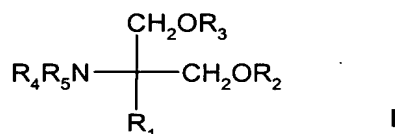
each of R<sub>3x</sub> and R<sub>4x</sub>, independently, is H, C<sub>1-4</sub>alkyl optionally substituted by halogen or acyl,

R<sub>5x</sub> is H, C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkoxy, and

R<sub>6x</sub> is C<sub>1-20</sub>alkanoyl substituted by cycloalkyl; cycloalkylC<sub>1-14</sub>alkoxy wherein the cycloalkyl ring is optionally substituted by halogen, C<sub>1-4</sub>alkyl and/or C<sub>1-4</sub>alkoxy; phenylC<sub>1-14</sub>alkoxy wherein the phenyl ring is optionally substituted by halogen, C<sub>1-4</sub>alkyl and/or C<sub>1-4</sub>alkoxy, being also C<sub>4-14</sub>alkoxy when R<sub>1x</sub> is C<sub>2-4</sub>alkyl substituted by OH, pentyloxy or hexyloxy when R<sub>1x</sub> is C<sub>1-4</sub>alkyl,

provided that R<sub>6x</sub> is other than phenyl-butylenoxy when either R<sub>5x</sub> is H or R<sub>1x</sub> is methyl, or a pharmaceutically acceptable salt thereof.

Claim 10. (New) The method of claim 6, wherein the S1P receptor agonist is selected from a compound of formula I



wherein R<sub>1</sub> is a straight- or branched (C<sub>12-22</sub>)carbon chain

- which may have in the chain a bond or a hetero atom selected from a double bond, a triple bond, O, S, NR<sub>6</sub>, wherein R<sub>6</sub> is H, alkyl, aralkyl, acyl or alkoxycarbonyl, and carbonyl, and/or
- which may have as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxyimino, hydroxy or carboxy; or

R<sub>1</sub> is

- a phenylalkyl wherein alkyl is a straight- or branched (C<sub>6-20</sub>)carbon chain or
- a phenylalkyl wherein alkyl is a straight- or branched (C<sub>1-30</sub>)carbon chain wherein said phenylalkyl is substituted by
- a straight- or branched (C<sub>6-20</sub>)carbon chain optionally substituted by halogen,
- a straight- or branched (C<sub>6-20</sub>)alkoxy chain optionally substituted by halogen,
- a straight- or branched (C<sub>6-20</sub>)alkenyloxy,
- phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl,
- cycloalkylalkyl substituted by C<sub>6-20</sub>alkyl,
- heteroarylalkyl substituted by C<sub>6-20</sub>alkyl,
- heterocyclic C<sub>6-20</sub>alkyl or
- heterocyclic alkyl substituted by C<sub>6-20</sub>alkyl,

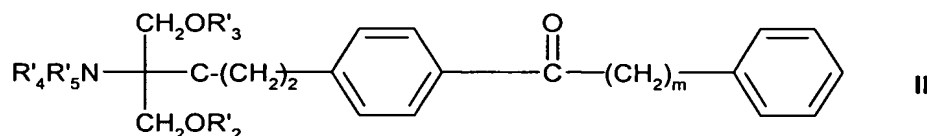
and wherein

the alkyl moiety may have

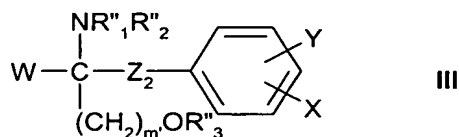
- in the carbon chain, a bond or a heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or  $\text{NR}_6$ , wherein  $\text{R}_6$  is as defined above, and
- as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxy or carboxy, and

each of  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$  and  $\text{R}_5$ , independently, is H,  $\text{C}_{1-4}$ alkyl or acyl;

a compound of formula II



wherein m is 1 to 9 and each of  $\text{R}'_2$ ,  $\text{R}'_3$ ,  $\text{R}'_4$  and  $\text{R}'_5$ , independently, is H, alkyl or acyl, a compound of formula III

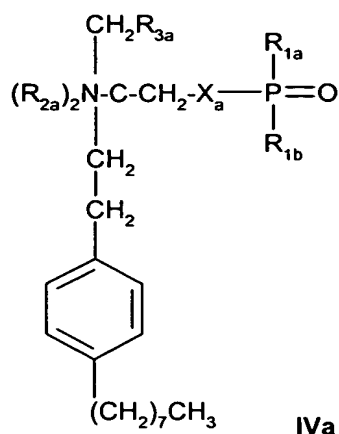


wherein W is H;  $\text{C}_{1-6}$ alkyl,  $\text{C}_{2-6}$ alkenyl or  $\text{C}_{2-6}$ alkynyl; unsubstituted or by OH substituted phenyl;  $\text{R}''_4\text{O}(\text{CH}_2)_n$ ; or  $\text{C}_{1-6}$ alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen,  $\text{C}_{3-8}$ cycloalkyl, phenyl and phenyl substituted by OH;

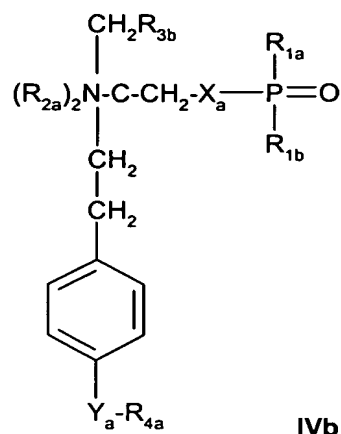
X is H or unsubstituted or substituted straight chain alkyl having a number p of carbon atoms or unsubstituted or substituted straight chain alkoxy having a number (p-1) of carbon atoms, e.g. substituted by 1 to 3 substituents selected from the group consisting of  $\text{C}_{1-6}$ alkyl, OH,  $\text{C}_{1-6}$ alkoxy, acyloxy, amino,  $\text{C}_{1-6}$ alkylamino, acylamino, oxo, halo $\text{C}_{1-6}$ alkyl, halogen, unsubstituted phenyl and phenyl substituted by 1 to 3 substituents selected from the group consisting of  $\text{C}_{1-6}$ alkyl, OH,  $\text{C}_{1-6}$ alkoxy, acyl, acyloxy, amino,  $\text{C}_{1-6}$ alkylamino, acylamino, halo $\text{C}_{1-6}$ alkyl and halogen; Y is H,  $\text{C}_{1-6}$ alkyl, OH,  $\text{C}_{1-6}$ alkoxy, acyl, acyloxy, amino,  $\text{C}_{1-6}$ alkylamino, acylamino, halo $\text{C}_{1-6}$ alkyl or halogen,  $\text{Z}_2$  is a single bond or a straight chain alkylene having a number of carbon atoms of q, each of p and q, independently, is an integer of 1 to 20, with the proviso of  $6 \leq p+q \leq 23$ , m' is 1, 2 or 3, n is 2 or 3,

each of  $\text{R}''_1$ ,  $\text{R}''_2$ ,  $\text{R}''_3$  and  $\text{R}''_4$ , independently, is H,  $\text{C}_{1-4}$ alkyl or acyl;

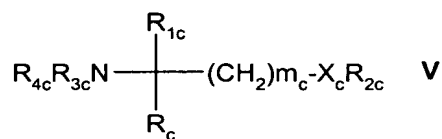
a compound of formula IVa or IVb



or



wherein  $\text{X}_a$  is O, S,  $\text{NR}_{1s}$  or a group  $-(\text{CH}_2)_{n_a}-$ , which group is unsubstituted or substituted by 1 to 4 halogen;  $n_a$  is 1 or 2,  $\text{R}_{1s}$  is H or  $(\text{C}_{1-4})$ alkyl, which alkyl is unsubstituted or substituted by halogen;  $\text{R}_{1a}$  is H, OH,  $(\text{C}_{1-4})$ alkyl or  $\text{O}(\text{C}_{1-4})$ alkyl wherein alkyl is unsubstituted or substituted by 1 to 3 halogen;  $\text{R}_{1b}$  is H, OH or  $(\text{C}_{1-4})$ alkyl, wherein alkyl is unsubstituted or substituted by halogen; each  $\text{R}_{2a}$  is independently selected from H or  $(\text{C}_{1-4})$ alkyl, which alkyl is unsubstituted or substituted by halogen;  $\text{R}_{3a}$  is H, OH, halogen or  $\text{O}(\text{C}_{1-4})$ alkyl wherein alkyl is unsubstituted or substituted by halogen; and  $\text{R}_{3b}$  is H, OH, halogen,  $(\text{C}_{1-4})$ alkyl wherein alkyl is unsubstituted or substituted by hydroxy, or  $\text{O}(\text{C}_{1-4})$ alkyl wherein alkyl is unsubstituted or substituted by halogen;  $\text{Y}_a$  is  $-\text{CH}_2-$ ,  $-\text{C}(\text{O})-$ ,  $-\text{CH}(\text{OH})-$ ,  $-\text{C}(=\text{NOH})-$ , O or S, and  $\text{R}_{4a}$  is  $(\text{C}_{4-14})$ alkyl or  $(\text{C}_{4-14})$ alkenyl; and a compound of formula V



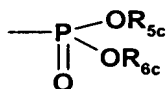
wherein

$m_c$  is 1, 2 or 3;

$\text{X}_c$  is O or a direct bond;

$\text{R}_{1c}$  is H; C1-6alkyl optionally substituted by OH, acyl, halogen, C3-10cycloalkyl, phenyl or hydroxy-phenylene; C2-6alkenyl; C2-6alkynyl; or phenyl optionally substituted by OH;

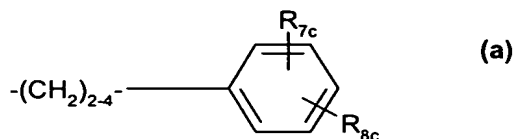
$\text{R}_{2c}$  is



wherein  $\text{R}_{5c}$  is H or  $\text{C}_{1-4}$ alkyl optionally substituted by 1, 2 or 3 halogen atoms, and  $\text{R}_{6c}$  is H or  $\text{C}_{1-4}$ alkyl optionally substituted by halogen;

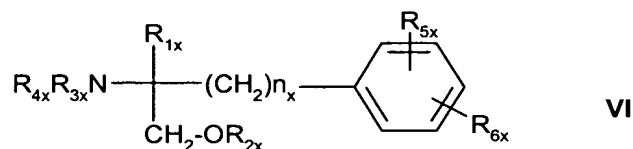
each of  $\text{R}_{3c}$  and  $\text{R}_{4c}$ , independently, is H,  $\text{C}_{1-4}$ alkyl optionally substituted by halogen, or acyl, and

$R_c$  is  $C_{13-20}$ alkyl which may optionally have in the chain an oxygen atom and which may optionally be substituted by nitro, halogen, amino, hydroxy or carboxy; or a residue of formula (a)



wherein  $R_{7c}$  is H,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkoxy, and  $R_{8c}$  is substituted  $C_{1-20}$ alkanoyl, phenyl $C_{1-14}$ alkyl wherein the  $C_{1-14}$ alkyl is optionally substituted by halogen or OH, cycloalkyl $C_{1-14}$ alkoxy or phenyl $C_{1-14}$ alkoxy wherein the cycloalkyl or phenyl ring is optionally substituted by halogen,  $C_{1-4}$ alkyl and/or  $C_{1-4}$ alkoxy, phenyl $C_{1-14}$ alkoxy- $C_{1-14}$ alkyl, phenoxy $C_{1-14}$ alkoxy or phenoxy $C_{1-14}$ alkyl,

$R_c$  being also a residue of formula (a) wherein  $R_{8c}$  is  $C_{1-14}$ alkoxy when  $R_{1c}$  is  $C_{1-4}$ alkyl,  $C_{2-6}$ alkenyl or  $C_{2-6}$ alkynyl, or a compound of formula VI



wherein

$n_x$  is 2, 3 or 4

$R_{1x}$  is H;  $C_{1-6}$ alkyl optionally substituted by OH, acyl, halogen, cycloalkyl, phenyl or hydroxy-phenylene;  $C_{2-6}$ alkenyl;  $C_{2-6}$ alkynyl; or phenyl optionally substituted by OH;

$R_{2x}$  is H,  $C_{1-4}$ alkyl or acyl

each of  $R_{3x}$  and  $R_{4x}$ , independently, is H,  $C_{1-4}$ alkyl optionally substituted by halogen or acyl,

$R_{5x}$  is H,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkoxy, and

$R_{6x}$  is  $C_{1-20}$ alkanoyl substituted by cycloalkyl; cycloalkyl $C_{1-14}$ alkoxy wherein the cycloalkyl ring is optionally substituted by halogen,  $C_{1-4}$ alkyl and/or  $C_{1-4}$ alkoxy; phenyl $C_{1-14}$ alkoxy wherein the phenyl ring is optionally substituted by halogen,  $C_{1-4}$ alkyl and/or  $C_{1-4}$ alkoxy,

$R_{6x}$  being also  $C_{4-14}$ alkoxy when  $R_{1x}$  is  $C_{2-4}$ alkyl substituted by OH, pentyloxy or hexyloxy when  $R_{1x}$  is  $C_{1-4}$ alkyl,

provided that  $R_{6x}$  is other than phenyl-butylenoxy when either  $R_{5x}$  is H or  $R_{1x}$  is methyl, or a pharmaceutically acceptable salt thereof.